SUPPLEMENTARY DATA

Online Supplement

Use of sodium-glucose cotransporter-2 inhibitors in patients with type 1 diabetes mellitus and rates of diabetic ketoacidosis

Christian Hampp[1], Richard Swain[1], Casie Horgan[2], Elizabeth Dee[2], Yandong Qiang[1], Sarah Dutcher[1], Andrew Petrone[2], Rong Chen Tilney[2],Judith C. Maro[2], Catherine A. Panozzo[2]

[1]Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD

[2]Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA

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Algorithms to detect diabetes type

- Type 1 diabetes-broad, required **only** the following:
    - A majority (>50%) of baseline codes for diabetes (ICD-9-CM: 250.x0-4; ICD-10-CM: E10.x, E11.x) occurring in any care setting is for type 1 diabetes (ICD-9-CM:250.x1, 250.x3; ICD-10-CM: E10.x). Baseline period is defined as [-365 to -5] days prior to the index SGLT-2 inhibitor or sitagliptin dispensing. The exclusion of index date and 5 days leading up to index date is intended to exclude claims with miscoding of type 1 diabetes as type 2 diabetes to allow for SGLT-2 insurance coverage.
- Type 1 diabetes-narrow, required **all** of the following:
    - A majority (>50%) of baseline codes for diabetes (ICD-9-CM: 250.x0-4; ICD-10-CM: E10.x, E11.x) occurring in any care setting is for type 1 diabetes (ICD-9-CM: 250.x1, 250.x3; ICD-10-CM: E10.x). Baseline period is defined as [-365 to -5] days prior to the index SGLT-2 inhibitor or sitagliptin dispensing. The exclusion of index date and 5 days leading up to index date is intended to exclude claims with miscoding of type 1 diabetes as type 2 diabetes to allow for SGLT-2 insurance coverage.
    - And: at least one dispensing for a short- or rapid-acting insulin during the baseline period. Baseline period is defined as [-365 to -1] day(s) prior to the index SGLT-2 inhibitor or sitagliptin dispensing.
    - And: no oral antidiabetic drug dispensing (other than metformin) during the baseline period. Baseline period is defined as [-365 to -1] day(s) prior to the index SGLT-2 inhibitor or sitagliptin dispensing.
- Type 2 diabetes:
    - Presence of ≥1 type 2 diabetes code(s) (ICD-9-CM: 250.x0, 250.x.2; ICD-10-CM: E11.x) and no type 1 diabetes code (ICD-9-CM: 250.x1, 250.x3; ICD-10-CM: E10.x) during baseline in any care setting. Baseline period is defined as [-365 to -5] days prior to the index SGLT-2 inhibitor of sitagliptin dispensing. The exclusion of index date and 5 days leading up to index date is intended to exclude claims with miscoding of type 1 diabetes as type 2 diabetes to allow for SGLT-2 insurance coverage.
    - Presence of ≥1 oral antidiabetic drug during baseline (other than SGLT-2inhibitor). Baseline period is defined as [-365 to -1] day(s) prior to the index SGLT-2 inhibitor or sitagliptin dispensing.

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Supplemental Table 1. Baseline characteristics of patients using SGLT-2 inhibitors or sitagliptin who meet criteria for type 1 diabetes

	Canagliflozin		Dapagliflozin		Empagliflozin		Sitagliptin	
	Type 1 diabetes-narrow	**Type 1 diabetes-broad**	**Type 1 diabetes-narrow**	**Type 1 diabetes-broad**	**Type 1 diabetes-narrow**	**Type 1 diabetes-broad**	**Type 1 diabetes-narrow**	**Type 1 diabetes-broad**
N	1,520	2,907	391	734	468	734	791	2,909
Mean Age	52.3	56.9	51.0	55.1	52.0	54.5	61.5	65.8
Age: <25 years	3.4%	2.1%	3.3%	1.9%	2.3%	1.6%	1.7%	0.9%
Age: 25-44 years	28.4%	19.5%	28.6%	20.2%	29.1%	23.6%	15.9%	8.8%
Age: 45-64 years	46.6%	44.8%	54.2%	53.8%	51.9%	53.0%	33.6%	30.7%
Age: >=65 years	21.7%	33.6%	13.8%	24.1%	16.7%	21.8%	48.7%	59.6%
Sex: Female	53.9%	49.6%	56.3%	50.7%	48.3%	48.6%	57.3%	52.3%
Sex: Male	46.1%	50.4%	43.7%	49.3%	51.7%	51.4%	42.7%	47.7%
Year (2013)	9.9%	10.8%	--	--	--	--	20.9%	23.8%
Year (2014)	32.0%	31.0%	36.1%	36.5%	6.4%	6.5%	28.7%	29.2%
Year (2015)	38.8%	38.5%	36.1%	34.2%	28.0%	29.7%	26.4%	25.5%
Year (2016)	16.2%	16.8%	17.1%	19.6%	33.1%	33.8%	18.6%	16.8%
Years (2017-2018)	3.2%	2.9%	10.8%	9.7%	32.5%	30.0%	5.5%	4.7%
Non-insulin antidiabetic drugs[1]								
Acarbose	--	0.4%	--	*****	--	*****	---	0.5%
Albiglutide	*****	*****	--	*****	*****	*****	*****	*****
Alogliptin	--	*****	--	*****	--	*****	--	--

[1] The narrow type 1 diabetes definition excluded patients with baseline oral AD drug use other than metformin and required ≥ 1 prescription for short- or rapid-acting insulin

*****Data are not presented due to a small cell size or to ensure a small cell cannot be recalculated through the cells presented.

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	Canagliflozin		Dapagliflozin		Empagliflozin		Sitagliptin	
	Type 1 diabetes-narrow	**Type 1 diabetes-broad**	**Type 1 diabetes-narrow**	**Type 1 diabetes-broad**	**Type 1 diabetes-narrow**	**Type 1 diabetes-broad**	**Type 1 diabetes-narrow**	**Type 1 diabetes-broad**
Canagliflozin	--	--	--	--	--	--	--	2.2%
Dapagliflozin	--	--	--	--	--	--	--	0.4%
Dulaglutide	*****	0.4%	*****	*****	3.0%	4.1%	*****	*****
Empagliflozin	--	--	--	--	--	--	--	*****
Exenatide	2.5%	4.3%	*****	3.4%	2.6%	3.1%	2.0%	1.7%
Glimiperide	--	8.9%	--	6.4%	--	5.9%	--	11.8%
Glipizide	--	8.1%	--	6.3%	--	4.5%	--	16.2%
Glyburide	--	3.7%	--	2.7%	--	1.9%	--	7.8%
Linagliptin	--	2.1%	--	2.3%	--	1.9%	--	--
Liraglutide	11.3%	12.0%	10.5%	12.7%	8.8%	10.1%	3.4%	2.6%
Metformin	30.8%	48.0%	23.3%	44.3%	28.0%	43.6%	40.6%	55.1%
Nateglinide	--	0.8%	--	*****	--	*****	--	1.0%
Pioglitazone	--	6.2%	--	6.4%	--	3.8%	--	6.8%
Repaglinide	--	0.9%	--	*****	--	*****	--	1.2%
Saxagliptin	--	3.1%	--	4.5%	--	1.6%	--	--
Sitagliptin	--	12.0%	--	11.2%	--	8.0%	--	--
Insulin – short and rapid acting								
Insulin lispro	51.9%	33.4%	53.5%	34.7%	63.5%	46.9%	44.5%	16.3%
Insulin regular, human	7.5%	7.9%	8.7%	8.0%	7.5%	6.7%	16.8%	10.2%
Insulin glulisine	6.9%	4.2%	11.5%	6.4%	5.3%	4.0%	3.2%	1.2%
Insulin aspart	45.0%	32.4%	40.2%	29.3%	41.0%	30.8%	51.3%	21.6%
Insulin lispro protamine	3.0%	2.8%	*****	2.6%	2.4%	2.9%	9.1%	3.6%

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	Canagliflozin		Dapagliflozin		Empagliflozin		Sitagliptin	
	Type 1 diabetes-narrow	**Type 1 diabetes-broad**	**Type 1 diabetes-narrow**	**Type 1 diabetes-broad**	**Type 1 diabetes-narrow**	**Type 1 diabetes-broad**	**Type 1 diabetes-narrow**	**Type 1 diabetes-broad**
Insulin – long acting								
Insulin glargine,human recombinant analog	38.1%	38.7%	39.4%	38.7%	38.5%	39.6%	54.7%	36.8%
Insulin NPH human isophane	4.2%	6.0%	3.8%	4.5%	*****	3.5%	9.5%	8.8%
Insulin detemir	17.6%	18.9%	16.1%	18.7%	13.5%	15.4%	22.1%	14.8%
Insulin aspart protamine human	1.5%	4.1%	*****	4.0%	*****	2.5%	5.4%	5.0%
Insulin degludec	0.9%	0.6%	*****	*****	3.6%	3.3%	*****	0.4%
Insulin pump	30.6%	17.3%	36.6%	21.3%	41.2%	27.7%	3.8%	1.6%
Diabetic Ketoacidosis diagnosis	5.6%	3.6%	5.4%	3.4%	4.1%	2.9%	6.7%	2.6%

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Supplemental Table 2. Baseline characteristics of patients who meet criteria fortype 2 diabetes

	Canagliflozin	Dapagliflozin	Empagliflozin	Sitagliptin
	Type 2 diabetes	**Type 2 diabetes**	**Type 2 diabetes**	**Type 2 diabetes**
N	229,836	60,910	78,420	482,451
Mean Age	62.1	59.3	59.8	67.2
Age: <25 years	0.1%	0.2%	0.1%	0.1%
Age: 25-44 years	8.7%	11.3%	10.0%	5.6%
Age: 45-64 years	44.6%	55.5%	56.0%	30.7%
Age: >=65 years	46.5%	33.1%	33.8%	63.6%
Sex: Female	47.0%	45.9%	43.0%	52.0%
Sex: Male	53.0%	54.1%	57.0%	48.0%
Year (2013)	6.7%	--	--	17.8%
Year (2014)	24.4%	25.9%	2.6%	24.4%
Year (2015)	36.1%	30.9%	18.3%	24.5%
Year (2016)	26.8%	29.0%	38.0%	25.0%
Years (2017-2018)	6.0%	14.2%	41.1%	8.3%
Select non-insulin antidiabetic drugs used during baseline				
Acarbose	1.0%	0.7%	0.6%	0.6%
Albiglutide	0.4%	0.8%	1.2%	0.1%
Alogliptin	0.4%	0.6%	0.6%	0.0%
Canagliflozin	--	--	--	2.9%
Dapagliflozin	--	--	--	0.7%
Dulaglutide	0.9%	1.9%	4.1%	0.3%
Empagliflozin	--	--	--	0.5%
Exenatide	5.3%	6.3%	4.5%	1.3%
Glimiperide	23.2%	20.7%	21.1%	19.9%
Glipizide	22.9%	19.7%	19.7%	27.3%
Glyburide	9.0%	8.1%	6.2%	10.6%
Linagliptin	6.6%	6.7%	8.0%	--
Liraglutide	11.2%	10.9%	10.6%	2.3%
Metformin	87.5%	88.9%	89.2%	84.4%
Nateglinide	1.1%	1.0%	0.7%	0.9%
Pioglitazone	12.3%	11.9%	10.4%	9.0%
Repaglinide	1.3%	1.0%	1.0%	0.9%
Saxagliptin	7.3%	8.8%	5.5%	--

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	Canagliflozin	Dapagliflozin	Empagliflozin	Sitagliptin
	Type 2 diabetes	**Type 2 diabetes**	**Type 2 diabetes**	**Type 2 diabetes**
Sitagliptin	30.2%	28.1%	24.7%	--
Insulin – short and rapid acting used during baseline				
Insulin lispro	5.6%	4.4%	6.6%	2.5%
Insulin regular, human	1.9%	1.5%	1.8%	1.7%
Insulin glulisine	0.4%	0.5%	0.3%	0.1%
Insulin aspart	7.0%	5.8%	5.3%	3.7%
Insulin lispro protamine	1.2%	0.9%	1.1%	0.4%
Insulin – long acting used during baseline				
Insulin glargine,human recombinant analog	16.5%	14.0%	15.6%	9.3%
Insulin NPH human isophane	1.7%	1.3%	2.0%	1.3%
Insulin detemir	8.5%	7.8%	7.5%	3.9%
Insulin aspart protamine human	1.5%	1.2%	1.0%	0.8%
Insulin degludec	0.2%	0.6%	1.3%	0.1%
Insulin pump	0.2%	0.2%	0.2%	0.1%
Diabetic Ketoacidosis diagnosis during baseline	0.2%	0.2%	0.2%	0.3%

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Supplemental Table 3. Age-and sex-specific rates of diabetic ketoacidosis among users (age 25+) of SGLT-2 inhibitors or sitagliptin with type 2 diabetes

	All SGLT-2 inhibitors			Sitagliptin (Control)		
	Type 2 diabetes			Type 2 diabetes		
	N	DKA events	DKA /100p-yrs	N	DKA events	DKA /100p-yrs
All patients[a]	368,596	652	0.41 (0.38-0.44)	481,839	758	0.34 (0.32-0.37)
Females						
All ages	169,344	336	0.49 (0.44-0.55)	250,299	470	0.42 (0.38-0.46)
25-44	15,798	46	0.83 (0.62-1.10)	12,793	29	0.63 (0.43-0.88)
45-64	79,585	157	0.47 (0.40-0.55)	70,942	137	0.45 (0.38-0.53)
≥65	73,961	133	0.45 (0.38-0.53)	166,564	304	0.39 (0.35-0.44)
Males						
All ages	199,252	316	0.35 (0.31-0.39)	231,540	288	0.27 (0.24-0.30)
25-44	18,932	32	0.43 (0.30-0.60)	14,160	17	0.30 (0.18-0.47)
45-64	100,629	183	0.39 (0.33-0.45)	77,306	93	0.26 (0.21-0.32)
≥65	79.691	101	0.28 (0.23-0.35)	140,074	178	0.27 (0.23-0.31)

[a] Including only patients with sex = “male” or “female”, excluding sex = “other”

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Supplemental Table 4. Age-and sex-specific rates of diabetic ketoacidosis among users (age 25+) of SGLT-2 inhibitors or sitagliptin with type 2 diabetes, stratified according to prior insulin exposure[a]

	All SGLT-2 inhibitors						Sitagliptin (Control)					
	Type 2 diabetes						Type 2 diabetes					
	Prior insulin			No prior insulin			Prior insulin			No prior insulin		
	N	DKA events	DKA /100p-yrs	N	DKA events	DKA /100p-yrs	N	DKA events	DKA /100p-yrs	N	DKA events	DKA /100p-yrs
All patients	98,112	290	0.69 (0.62-0.78)	270,869	364	0.31 (0.28-0.35)	75,639	252	0.79 (0.70-0.90)	407,243	507	0.27 (0.25-0.29)
Females												
All ages	47,072	154	0.82 (0.71-0.97)	122,454	183	0.37 (0.32-0.42)	41,695	152	0.88 (0.75-1.03)	209,154	318	0.33 (0.30-0.37)
25-44	4,481	21	1.31 (0.83-1.97)	11,346	25	0.63 (0.42-0.92)	2,275	13	1.67 (0.93-2.79)	10,547	16	0.41 (0.45-0.66)
45-64	23,717	83	0.84 (0.67-1.04)	55,947	75	0.32 (0.25-0.40)	13,277	54	1.02 (0.77-1.32)	57,817	83	0.33 (0.26-0.41)
≥65	18,874	50	0.69 (0.52-0.91)	55,161	83	0.37 (0.30-0.46)	26,143	85	0.77 (0.62-0.94)	140,790	219	0.33 (0.29-0.37)
Males												
All ages	51,040	136	0.59 (0.49-0.69)	148,415	181	0.27 (0.23-0.31)	33,944	100	0.69 (0.56-0.83)	198,089	189	0.20 (0.18-0.24)
25-44	4,593	16	0.87 (0.51-1.38)	14,361	16	0.28 (0.17-0.45)	2,093	*****	0.78 (0.32-1.62)	12,094	*****	0.22 (0.12-0.39)
45-64	26,889	84	0.66 (0.53-0.81)	73,831	99	0.29 (0.23-0.65)	12,289	*****	0.80 (0.59-1.07)	65,178	*****	0.17 (0.12-0.22)
≥65	19,558	36	0.42 (0.30-0.57)	60,223	66	0.25 (0.19-0.31)	19,562	51	0.61 (0.46-0.79)	120,817	128	0.22 (0.18-0.26)

[a]Because cohorts are formed independently, patients may be eligible for inclusion in both the 'type 2 diabetes-Prior Insulin' and 'type 2 diabetes-No Prior Insulin' cohorts. If a patient had one valid SGLT-2 exposure with no insulin use in the prior 365 days, and a subsequent valid SGLT-2 exposure with evidence of prior insulin, they would be counted once in each cohort. As a result, the sum of N counts from the 'Type 2 diabetes-Prior Insulin' and 'type 2 diabetes-No Prior Insulin' cohorts may exceed that of the overall 'type 2 diabetes' cohort.

*****Data are not presented due to a small cell size or to ensure a small cell cannot be recalculated through the cells presented.

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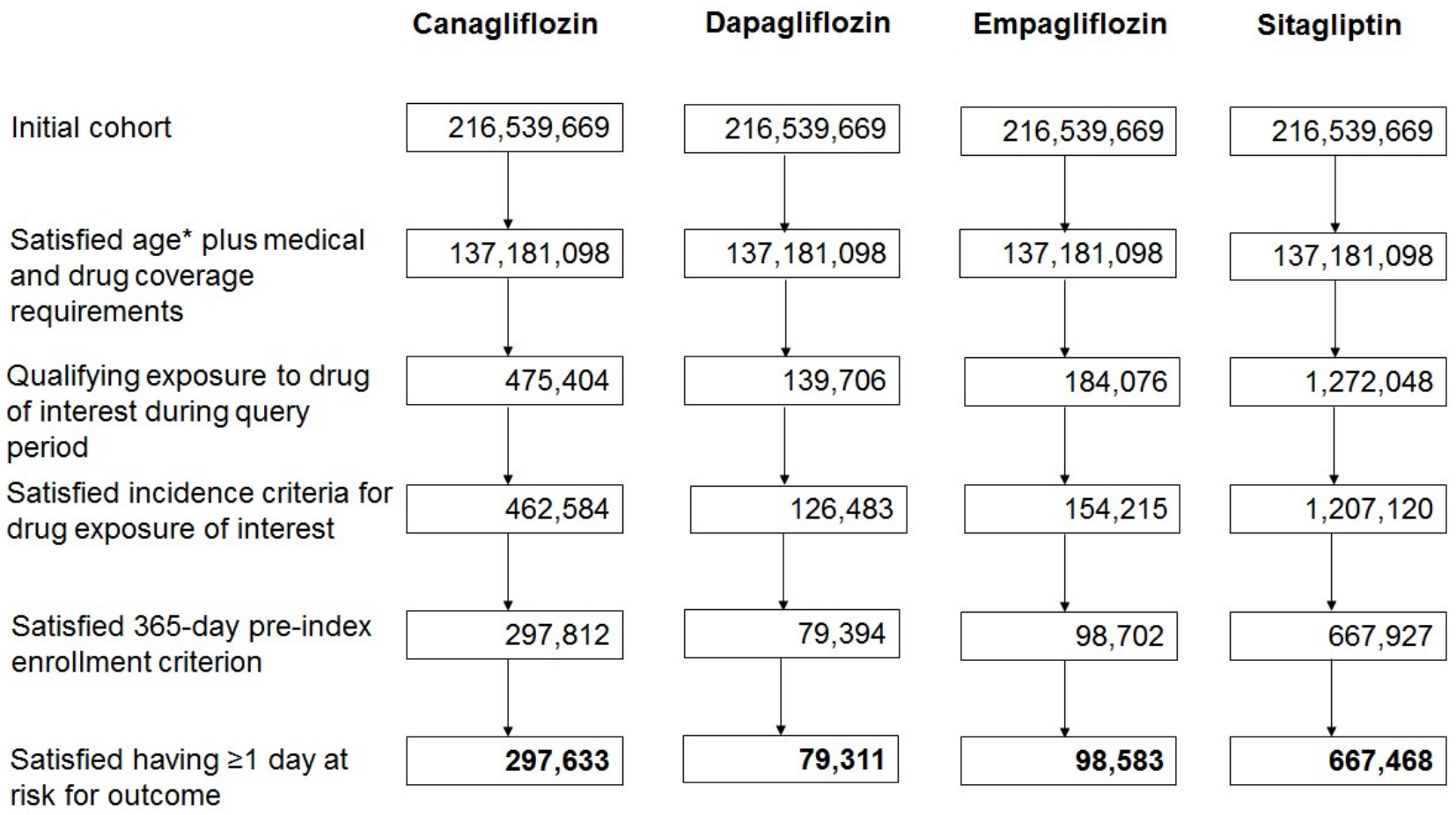
Supplemental Figure 1. Cohort attrition for canagliflozin, dapagliflozin, empagliflozin, and sitagliptin user groups, irrespective of diabetes diagnosis or type, Sentinel System, March 1, 2013- June 30, 2018



*Although this study did not make any age restrictions, small numbers of members with potentially implausible ages (<0 years or >110 years) were removed in this step.

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Supplemental Figure 2.Rates of diabetic ketoacidosis per 100 person-years, by diabetes type; error bars indicate 95% confidence intervals